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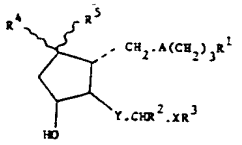
(54) PROSTANOIC ACID DERIVATIVES

(71) We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, Imperial Chemical House, Millbank, London SW1P 3JF, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel prostanoic acid derivatives, and in particular it relates to novel 11-*epi*-prostanoic acid derivatives which possess luteolytic activity. The new compounds are therefore advantageous when used as contraceptives or for control of the oestrous cycle in animals. The compounds may also be useful for the induction of labour, or as hypotensives, for the relief of bronchospasm, or as inhibitors of gastric secretion or of blood platelet aggregation.

According to the invention there is provided an 11-*epi*-prostanoic acid derivative of the formula:



I

wherein either R^1 is a carboxy or hydroxymethyl radical or an alkoxycarbonyl radical of 2 to 11 carbon atoms, R^4 is a hydroxy radical and R^5 is a hydrogen atom, or R^1 is a carboxy radical or an alkoxycarbonyl radical of 2 to 11 carbon atoms and R^4 and R^5 together form an oxo radical, R^2 is a hydroxy radical or an alkoxy radical of 1 to 4 carbon atoms, Y is an ethylene or *trans*-vinylene radical, either A is an ethylene or vinylene radical and X is an alkylideneoxy radical of 1 to 6 carbon atoms wherein the alkylidene is bonded to —CHR^2— and the oxygen is bonded to R^3, or an alkylene radical of 1 to 6 carbon atoms, or A is a vinylene radical and X is a direct bond, and R^3 is a phenyl or naphthyl radical which is unsubstituted or which bears one or two substituents selected from halogen atoms, nitro, hydroxy, phenyl or trifluoromethyl radicals, alkyl, alkenyl or alkoxy radicals each of up to 5 carbon atoms, or dialkylamino radicals wherein each alkyl is of 1 to 3 carbon atoms, and, for those compounds wherein R^1 is the carboxy radical, the pharmaceutically or veterinarily acceptable salts thereof.

A suitable value for R^1 when it is an alkoxycarbonyl radical is, for example, a

methoxycarbonyl, ethoxycarbonyl, butoxycarbonyl, hexyloxycarbonyl or decyloxycarbonyl radical, especially such an alkoxycarbonyl radical of up to 6 carbon atoms.

A suitable value for A^2 when it is an alkoxy radical is, for example, a methoxy, ethoxy, propoxy or butoxy radical.

A suitable value for X when it is an alkylideneoxy radical is, for example, a methyleneoxy, ethylideneoxy (—$CH(CH_3)$. O—), isopropylideneoxy (—$C(CH_3)_2$. O—), 1-methylpropylideneoxy (—$C(CH_3)(C_2H_5)$. O—) or 1-ethylpropylideneoxy (—$C(C_2H_5)_2$. O—) radical, and a suitable value for X when it is an alkylene radical is, for example, a methylene, ethylidene, isopropylidene, propylidene, 1-methylpropylidene, 1-ethylpropylidene, ethylene, 1-methylethylene [—$CH(CH_3)$. CH_2—], 1,1-dimethylethylene [—$C(CH_3)_2$. CH_2—], 2-methylethylene [—CH_2 . $CH(CH_3)$—] or trimethylene radical.

A suitable value for a halogen substituent in R^3 is, for example, a chlorine, bromine or fluorine atom, and a suitable value for alkyl, alkenyl or alkoxy substituent in R^3 is, for example, a methyl, ethyl, propyl, allyl, methoxy, ethoxy or propoxy radical. A suitable value for a dialkylamino substituent in R^3 is, for example, a dimethylamino radical.

A suitable pharmaceutically or veterinarily acceptable salt is, for example, an ammonium, alkylammonium containing 1 to 4 alkyl substituents each of 1 to 6 carbon atoms, alkanolammonium containing 1 to 3 2-hydroxyethyl radicals, or alkali metal salt, for example a triethyl ammonium, ethanolammonium, diethanolammonium, sodium or potassium salt.

It will be observed that the compounds of the formula I contain at least four asymmetric carbon atoms, namely carbon atoms 8, 11, 12 and 15, the relative configuration of the first three of which are fixed, so that it is clear that the compounds may exist in at least two optically active forms. It is to be understood that the useful properties of the racemates (comprising the compound of the formula I and its mirror image) described in this specification may be present to differing extents in the optical isomers, and that this invention relates to the racemic form and to any optically active form which possesses the same useful properties, it being a matter of common general knowledge how the optically active forms may be obtained and their respective biological properties determined. It is also to be understood that this invention relates to both C—15 epimers, that is, the epimers at the —CHR^2— carbon atom of the lower side-chain.

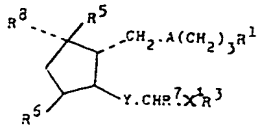
A preferred group of prostane derivatives of the invention comprises those compounds wherein R^1 is a carboxy, hydroxymethyl, methoxycarbonyl or ethoxycarbonyl radical, R^2 is a hydroxy radical, A is a *cis*-vinylene radical, Y is a *trans*-vinylene radical, X is a direct bond or a methyleneoxy radical, and R^3 is a chlorophenyl or trifluoromethylphenyl radical.

A preferred value for R^3, when X is a methyleneoxy radical, is a 3-chlorophenyl or 3-trifluoromethylphenyl radical, and a preferred value for R^3 when X is a direct bond, is a 4-trifluoromethyl radical.

Particular 11-*epi*-prostanoic acid derivatives of the invention are 16-(3-chlorophenoxy) - 9α,11β,15α - trihydroxy - 17,18,19,20 - tetranor - 5 - *cis*,13 - *trans*-prostadienoic acid, 16 - (3 - chlorophenoxy) - 9β,11β,15α - trihydroxy - 17,18,19,20-tetranor - 5 - *cis*,13 - *trans* - prostadienoic acid, methyl 16 - (3 - chlorophenoxy)-9α,11β,15α - trihydroxy - 17,18,19,20 - tetranor - 5 - *cis*,13 - *trans* - prostadienoate, 16 - (3 - chlorophenoxy) - 17,18,19,20 - tetranor - 5 - *cis*,13 - *trans* - prostadien-1,9α,11β,15α - tetraol, 16 - (3 - chlorophenoxy) - 11β,15 - dihydroxy - 9 - oxo-17,18,19,20 - tetranor - 5 - *cis*,13 - *trans* - prostadienoic acid and 9α,11β,15α-trihydroxy - 15 - (4 - trifluoromethylphenyl) - 16,17,18,19,20 - pentanor - 5 - *cis*,13-*trans*-prostadienoic acid.

The 11-*epi*-prostanoic acid derivative of the invention may be manufactured by methods known in themselves for the manufacture of chemically analogous compounds. Thus, according to a further feature of the invention there is provided a process for the manufacture of an 11-*epi*-prostanoic acid derivative of the invention which comprises:—

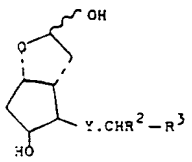
(a) for those compounds wherein R^1 is a carboxy radical, R^4, when it is a hydrogen atom, is in the α-configuration and X is other than a direct bond, the hydrolysis of a compound of the formula:—



II

wherein R^1, R^3, A and Y have the meanings defined above, X' has any of the meanings given above for X except a direct bond, R^6 is a tetrahydropyran-2-yloxy or C_{4-10} alkoxydialkylmethoxy radical, for example a 1-methoxy-1-methylethoxy radical, R^7 is an alkoxy radical of 1 to 4 carbon atoms or a tetrahydropyran-2-yloxy or C_{4-10} alkoxydialkylmethoxy radical, for example a 1-methoxy-1-methylethoxy radical, and either R^8 is a hydroxy radical or a tetrahydropyran-2-yloxy radical and R^5 is a hydrogen atom, or R^8 and R^5 together form an oxo radical; or R^6 is a hydroxy radical or an aroyloxy radical of up to 15 carbon atoms, R^7 is hydroxy radical and R^8 is an aroyloxy radical of up to 15 carbon atoms, whereafter when a salt is required, the product so obtained is reacted with a base; or

(b) for those compounds wherein R^1 is a carboxy radical, R^4 is an α-hydroxy radical, R^5 is a β-hydrogen atom, A is a vinylene radical and X is a direct bond, the reaction of a lactol of the formula:—



III

wherein R^2 and R^3 have the meanings defined above, with a (4-carboxybutyl)-triphenylphosphonium salt, for example the bromide, in the presence of a strong base, whereafter when a salt is required, the product so obtained is reacted with a base; or

(c) for those compounds wherein R^1 is an alkoxycarbonyl radical, the reaction of the corresponding compound of the formula I wherein R^1 is a carboxy radical, with a diazoalkane of 1 to 10 carbon atoms, or of a salt thereof, for example a silver or sodium salt, with an alkyl halide, for example an alkyliodide; or

(d) for those compounds wherein R^1 is a hydroxymethyl radical, R^4 is a hydroxy radical and R^5 is a hydrogen atom, the reduction of a corresponding compound of the formula I wherein R^1 is an alkoxycarbonyl radical, for example with a complex metal hydride such as lithium aluminium hydride; or

(e) for those compounds wherein R^2 is an alkoxy radical, the reaction of the corresponding compound of the formula I wherein R^2 is a hydroxy radical with an alkyl halide of 1 to 4 carbon atoms, for example an alkyl iodide, in the presence of a strong base, for example sodium hydride; or

(f) for those compounds wherein A is a *trans*-vinylene radical, the separation of a mixture comprising the said compound wherein A is a *trans*-vinylene radical and the corresponding compound wherein A is a *cis*-vinylene radical.

The hydrolysis in process (a) may be carried out with an acid, for example aqueous acetic acid or a sulphonic acid, for example toluene-*p*-sulphonic acid in a C_{1-4} alkanol when R^6 or R^7 is tetrahydropyran-2-yloxy radical, or buffered citric acid (e.g. pH 3) when R^6 or R^7 is an alkoxydialkylmethoxy radical, or it may be carried out with a base, for example an alkali metal carbonate such as potassium carbonate, when R^6 or R^7 is an aroyloxy radical, and it may be carried out at ambient temperature or at an elevated temperature of up to 60° C.

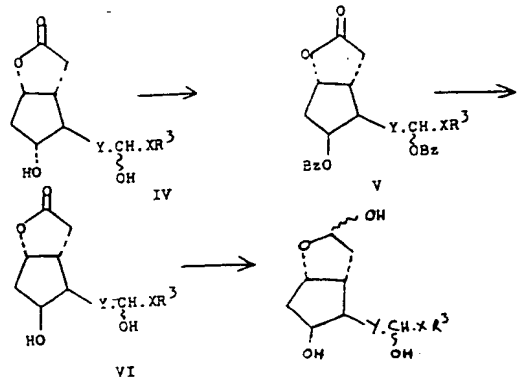
In process (b), when the strong base used is a sodium base, for example methanesulphinylmethyl sodium in dimethyl sulphoxide, or potassium t-butoxide, the product I obtained is one wherein, substantially completely, A is *trans*-vinylene, whereas if n-butyl-lithium in sulpholane is used as the strong base, the product obtained is one which contains a mixture of the compound wherein A is *trans*-vinylene and the compound wherein A is *cis*-vinylene, which mixture may be separated into its components by process (f) above.

In process (f), a suitable method for the separation of the 5-*trans* compound from a mixture of 5-*trans* and 5-*cis* compounds is by chromatography, for example on silica gel impregnated with silver nitrate, but other conventional methods of separating *cis*-*trans* mixtures may also be used, for example fractional crystallisation.

The starting material of the formula III, used in the process of the invention,

wherein R^2 is a hydroxy radical may be obtained by reacting a lactone IV with an azodicarboxylate ester in the presence of triphenylphosphine and benzoic acid to give the dibenzoate V which is hydrolysed to the diol VI. Reduction of the lactone with di-isobutyl aluminium hydride gives the required starting material III, (R^2=hydroxy).

Many of the required lactones of the formula IV are known compounds, and any others which are novel may be prepared by methods completely analogous to those used in the preparation of the known lactones of the formula IV.



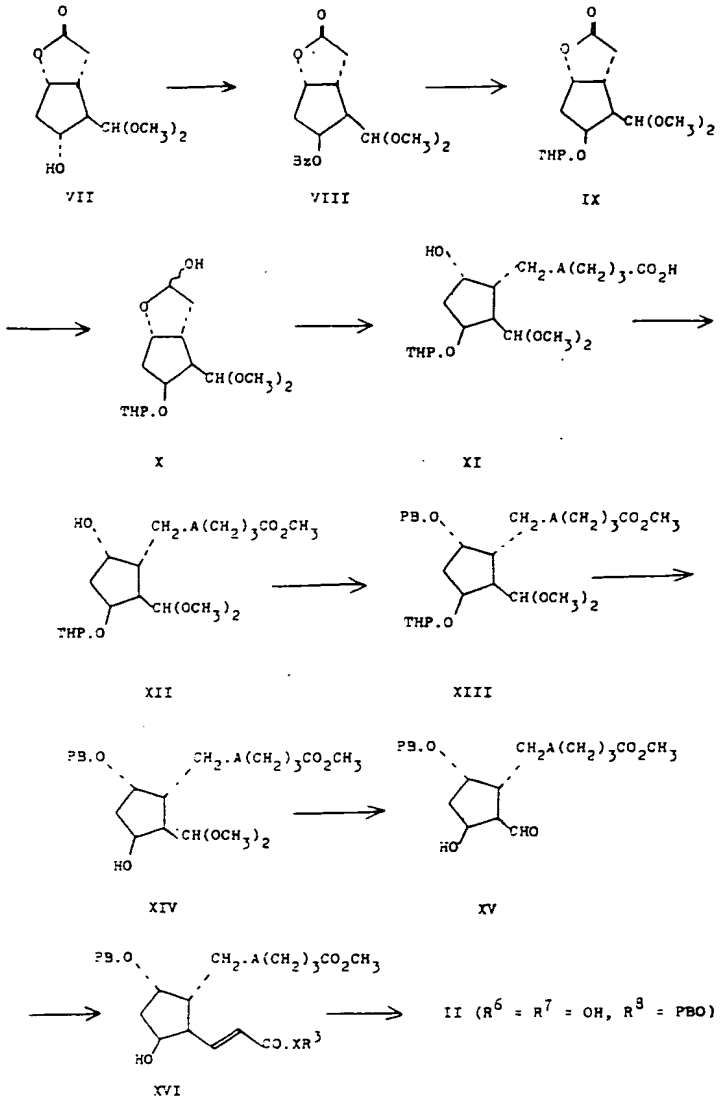
The starting material of the formula III wherein R^2 is an alkoxy radical may be obtained by reacting the corresponding compound VI with an alkyl halide, for example an alkyl bromide or iodide, in the presence of one equivalent of a strong base, for example sodium hydride, followed by the reduction of the product so obtained with di-isobutyl aluminium hydride, as described above, to give the required starting material III (R^2=alkoxy).

The starting material of the formula II, used in the process of the invention, wherein A is a vinylene radical, R^6 and R^7 are each a tetrahydropyran-2-yloxy radical, and R^8 is a hydroxy radical, may be obtained by reacting the corresponding compound VI with dihydropyran, to give a bis-(tetrahydropyran-2-yl ether), which is reduced with di-isobutyl aluminium hydride, as described above for compound VI, and the resulting lactol is reacted with a (4-carboxybutyl)triphenylphosphonium salt, as described above for a lactol III, to give a starting material II wherein A is *cis*-vinylene, if methanesulphinylmethyl sodium or potassium t-butoxide is used as the strong base or a mixture of compounds of the formula II wherein A is *trans*-vinylene and *cis*-vinylene, if n-butyl-lithium in sulpholane is used as the strong base, from which mixture the starting material II wherein A is *trans*-vinylene may be obtained by chromatography on silica gel impregnated with silver nitrate.

Corresponding starting materials of the formula II wherein R^6 and R^7 are each an alkoxydialkylmethoxy radical, may be prepared similarly, using an alkoxyalkene, for example 2-methoxypropene, in place of dihydropyran.

The starting material of the formula II wherein R^6 and R^7 are each a tetrahydropyran-2-yloxy radical and R^5 and R^8 together form an oxo radical, may be obtained by oxidation of the corresponding compound II wherein R^8 is a hydroxy radical, for example with Jones' reagent.

The starting material of the formula II, used in the process of the invention, wherein Y is a *trans*-vinylene radical, R^8 is an aroyloxy radical and R^6 and R^7 are each a hydroxy radical, may be obtained by treating the known lactone, 4β-dimethoxymethyl-2,3,3aβ,6aβ-tetrahydro-5α-hydroxy-2-oxocyclopenteno[b]furan (VII) with an azodicarboxylic ester in the presence of triphenylphosphine and benzoic acid, to give the benzoate of the C—5 epimer of VII (VIII), which is hydrolysed and then protected as the tetrahydropyranyl ether (IX). The lactone is reduced with di-isobutyl aluminium hydride to the lactol X, and the lactol is reacted with a phosphonium salt of the formula $Ph_3P(CH_2)_4 . COOH . Br^-$ in the presence of a strong base, to give a cyclopentanol derivative XI, wherein A is *cis*-vinylene if methanesulphinylmethyl sodium or potassium t-butoxide is used as the strong base, or a mixture of cyclopentanol derivatives XI wherein A is *cis*-vinylene and *trans*-vinylene when n-butyl-lithium in sulpholane is used as the strong base, from which mixture the cyclopentanol derivative XI



Bz = benzoyl, THP = tetrahydropyran-2-yl, PB = 4-phenylbenzoyl

wherein A is the *trans*-vinylene radical may be separated by chromatography on silica gel impregnated with silver nitrate. Alternatively, the mixture may be processed through one or more subsequent steps of the synthesis, and the corresponding *trans* intermediate may be separated at any convenient subsequent stage. A cyclopentanol derivative XI is converted by reaction with diazomethane to the methyl ester XII. The methyl ester XII is reacted with an acylating agent derived from an aroic acid, for example 4-phenylbenzoyl chloride, to give a 4-phenylbenzoate ester XIII, which is selectively hydrolysed in two steps, first to remove the tetrahydropyranyl protecting group (XIV), and then to hydrolyse the acetal to give the aldehyde (XV). The aldehyde XV is treated with a phosphonate $(CH_3O)_2PO.CH_2CO.XR^3$ or a phosphorane $Ph_3P{:}CH.CO.XR^3$ in the presence of a strong base to give the enone XVI, reduction of which with aluminium tri-isopropoxide or di-isobornyloxy aluminium isopropoxide gives the required starting material II wherein A is a vinylene radical, Y is *trans*-vinylene, $R^6 = R^7 =$ hydroxy, and $R^8 =$ aroyloxy.

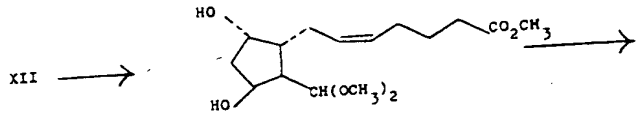
The starting material of the formula II, used in the process of the invention, wherein A is a vinylene radical, Y is a *trans*-vinylene radical, R^6 and R^8 are each an aroyloxy radical and R^7 is a hydroxy radical may be obtained from the methyl ester XII by selective hydrolysis of the tetrahydropyranyl radical, for example with toluene-

p-sulphonic acid in tetrahydrofuran, to a diol XVII, which is reacted with an acylating agent derived from an aroic acid, for example 4-phenylbenzoyl chloride, to give a bis-(phenylbenzoate ester) XVIII, which is selectively hydrolysed with dilute aqueous acid to the corresponding aldehyde XIX. The aldehyde XIX is reacted with a phosphonate or phosphorane as described above to give an enone XX, which is reduced, as described above for similar enones XVI, to the required starting material II ($R^6 = R^8 =$ aroyloxy, $R^7 =$ hydroxy).

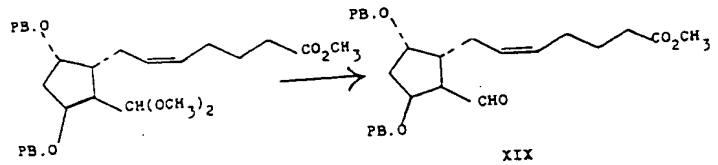
Starting materials of the formula II wherein Y is an ethylene radical and either R^6 and R^7 are each a hydroxy radical and R^8 is an aroyloxy radical, or R^7 is a hydroxy radical and R^6 and R^8 are each an aroyloxy radical, may be obtained by reducing respectively an enone XVI or an enone XX with, for example, sodium borohydride to give a mixture of 13,14-*trans* and 13,14-dihydro enols, from which the 13,14-dihydro enol (II, Y = ethylene) may be separated by conventional procedures.

Starting materials of the formula II wherein A is an ethylene radical may be obtained by hydrogenation of a corresponding starting material II wherein A is a *cis*-vinylene radical, or by hydrogenation of an intermediate of the formula XIV or XVIII, and using the hydrogenated intermediate in place of XIV or XVIII in the subsequent stages of the synthesis described above.

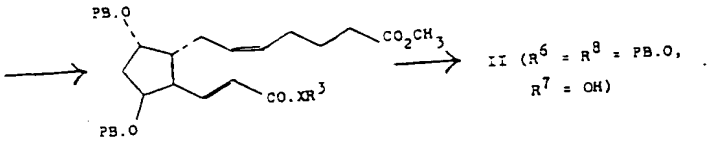
In an alternative synthesis, the intermediate XIV used in the above process may be obtained by treating the



XVII

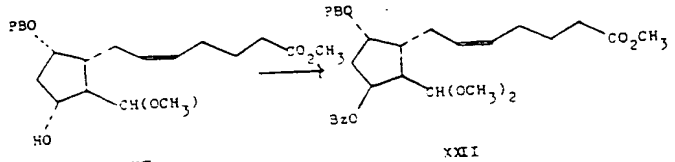


XVIII XIX



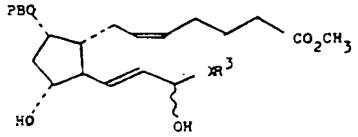
XX

known compound XXI with an azodicarboxylate ester, as described above, to give a di-ester XXII which is converted *via* intermediate analogous to XV and XVI to the required starting material II ($R^6 =$ benzoyloxy, $R^7 =$ hydroxy, $R^8 =$ 4-phenylbenzoyloxy).



XXI XXII

In a further alternative synthesis, a starting material of the formula II ($R^6 =$ benzoyloxy, $R^7 =$ hydroxy, $R^8 =$ 4-phenylbenzoyloxy) may be obtained by treating a compound of the formula:—



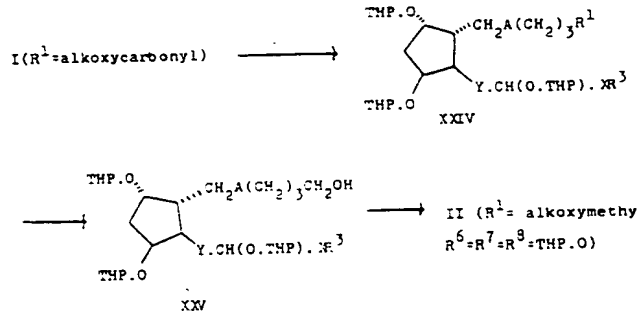
XXIII

with an azodicarboxylate ester as described above, to give a starting material of the formula II (R^6 = benzoyloxy, R^7 = hydroxy, R^8 = 4-phenylbenzoyloxy).

Compounds of the formula XXIII are known for certain values of $-XR^3$, for example where $-XR^3$ is 3-chlorophenoxy, and corresponding compounds for other values of $-XR^3$ may be manufactured in a completely analogous manner.

Starting materials of the formula II wherein R^1 is a carboxy or hydroxymethyl radical may be obtained from the corresponding compound wherein R^1 is an alkoxycarbonyl radical by, respectively, saponification or complex metal hydride reduction, for example with lithium aluminium hydride.

Starting materials of the formula II wherein R^1 is an alkoxycarbonyl radical may be obtained from an 11-*epi*-prostanoic acid derivative of the invention of the formula I wherein R^1 is an alkoxycarbonyl radical by reaction with 2,3-dihydropyran to give a tris(tetrahydropyranyl ether) XXIV which is reduced with lithium aluminium hydride to a hydroxymethyl compound XXV which in turn is alkylated to give a starting material II (R^1 = alkoxymethyl, $R^6 = R^7 = R^8$ = tetrahydropyran-2-yloxy).



THP = tetrahydropyran-2-yl.

As stated above, the compounds of the invention possess luteolytic properties. For example, 16 - (3 - chlorophenoxy) - 9α,11β,15α - trihydroxy - 17,18,19,20-tetranor-5-*cis*,13-*trans*-prostadienoic acid is approximately 500 times as active as natural prostaglandin $F_{2\alpha}$ in a luteolytic test in the hamster (oral dosing), but possesses only 1/12 of the smooth muscle stimulant activity of the natural compound. The compounds of the invention are therefore more selective than the natural compound in terms of luteolytic activity. No indication of toxicity to small animals has been noted at the luteolytically effective doses tested.

The compounds of the invention are therefore useful, for example, for the induction of labour in childbirth, and for this purpose are used in the same way as it is known to use the naturally-occurring prostaglandins E_1 and E_2, that is to say, by administering a sterile, substantially aqueous solution containing from 0.01 to 10 μg/ml., preferably 0.01 to 1 μg./ml. of active compound, by intravenous, extraovular or intra-amniotic administration until labour commences. Also, for this purpose, the compounds of the invention may be used in combination, or concurrently, with a uterine stimulant, for example oxytocin, in the same way that it is known to use prostaglandin $F_{2\alpha}$ in combination, or concurrently, with oxytocin for the induction of labour.

When a compound of the invention is to be used for the control of the oestrus cycle in animals, it may be used in combination, or concurrently, with a gonadotrophin, for example PMSG (pregnant mare serum gonadotrophin) or HCG (human chorionic gonadotrophin) to hasten the onset of the next cycle.

Thus, according to a further feature of the invention there is provided a pharmaceutical or veterinary composition comprising an 11-*epi*-prostanoic acid derivative of the invention, together with a pharmaceutically or veterinarily acceptable diluent or carrier.

The compositions may be in a form suitable for oral administration, for example tablets or capsules, in a form suitable for inhalation, for example an aerosol or a

solution suitable for spraying, in a form suitable for parenteral administration, for example sterile injectable aqueous or oily solutions or suspensions, or in the form of a suppository, suitable for anal or vaginal use.

The compositions of the invention may be prepared by conventional means, and may incorporate conventional excipients.

The invention is illustrated, but not limited by the following Examples.

Example 1.

A solution of 16-(3-chlorophenoxy)-9α-hydroxy-11β,15α-bis(tetrahydropyran-2-yloxy)-17,18,19,20-tetranor-5-*cis*,13-*trans*-prostadienoic acid (108 mg.) in 2 mls. of a 2:1 v/v mixture of acetic acid and water, was stirred at 50° C. for 4 hours. The solvents were evaporated, the residue was dissolved in dilute aqueous sodium bicarbonate solution (2 ml.), the solution was extracted with ethyl acetate (3 × 2 ml.) and the extracts were discarded. The aqueous solution was acidified to pH 3—4 with 2N aqueous oxalic acid and the acidified solution was extracted with ethyl acetate (4 × 5 ml.). The ethyl acetate extracts were washed with a 1:1 v/v mixture of saturated brine and water, and were then dried. After evaporation of the ethyl acetate, the residue consisted of 16 - (3 - chlorophenoxy) - 9α,11β,15α - trihydroxy - 17,18,19,20-tetranor-5-*cis*,13-*trans*-prostadienoic acid. Thin-layer chromatography on silica gel plates, supplied commercially by Merck of Darmstadt, using a mixture of 3% v/v acetic acid in ethyl acetate as the developing solvent, gave the pure compound, $R_F = 0.2$. The n.m.r. spectrum in deuteriated acetone showed the following characteristic bands (δ values):—

6.9—7.2, broad multiplet, 4 aromatic protons,

5.2—6.1, broad multiplets, 4 olefinic and 4 exchangeable protons,

3.95—4.5 broad multiplets, 5H, >C*H* . O-protons.

The mass spectrum of the tetra(trimethylsilyl) derivative showed $(M—CH_3)^+ = 697.2990$, (calculated for $C_{34}H_{61}ClO_6Si_4 = 697.3001$).

The bis(tetrahydropyranyl ether) used as starting material may be obtained as follows:

To a solution of 4β - [4 - (3 - chlorophenoxy) - 3β - hydroxybut - 1 - *trans*-enyl] - 2,3,3aβ,6aβ - tetrahydro - 5α - hydroxy - 2 - oxocyclopenteno[b]furan (838 mg.), triphenylphosphine (1.63 g.) and benzoic acid (758 mg.) in tetrahydrofuran (15 ml.) was added dropwise during 10 minutes diethyl azodicarboxylate (1.06 g.). After 45 minutes, the solvent was removed by evaporation, and the residue was extracted with ethyl acetate (3 × 30 ml.). The combined extracts were washed successively with sodium bicarbonate solution and brine, and dried, and the solvents were evaporated to give the bis-benzoate ester, 5β-benzoyloxy-4β-[3α-benzoyloxy-4-(3-chlorophenoxy)but - 1 - *trans* - enyl] - 2,3,3aβ,6aβ - tetrahydro - 2 - oxocyclopenteno-[b]furan, $R_F = 0.6$ (5% ethyl acetate in methylene dichloride).

To a solution of the bis-benzoate ester (1.03 g.) in a mixture of methanol and methylene dichloride (2:1) was added anhydrous potassium carbonate (578 mg.). The mixture was stirred for 6 hours at room temperature, acidified to pH 5 with 1N hydrochloric acid, and diluted with ethyl acetate (100 ml.). The mixture was washed successively with saturated sodium bicarbonate solution and brine, the organic phase was separated and dried, and the solvents were evaporated under reduced pressure. The crude product was chromatographed on MFC silica gel, using ethyl acetate in methylene dichloride as eluant, to yield the diol, 4β-[4-(3-chlorophenoxy)-3α-hydroxybut-1-*trans*-enyl]-2,3,3aβ,6aβ-tetrahydro-5β-hydroxy-2-oxocyclopenteno[b]furan, $R_F = 0.4$ (ethyl acetate). The n.m.r. spectrum (in deuterated chloroform) showed the following characteristic bands (δ values):—

6.8—7.6, broad multiplets, 4 aromatic protons,

5.8—6.0, 2 olefinic protons,

3.7—5.2, broad multiplets, 5H, >CH . O— protons

To a solution of the diol (215 mg.) in methylene dichloride (8 ml.) under an atmosphere of nitrogen were added successively redistilled 2,3-dihydropyran (0.58 ml.) and a solution of anhydrous toluene-*p*-sulphonic acid in tetrahydrofuran (0.6 ml. of a 1% w/v solution). After 10 minutes, pyridine (3 drops) was added, followed by ethyl acetate (50 ml.). The solution was washed successively with saturated sodium bicarbonate solution and saturated brine, and was dried. Evaporation of the solvents gave a bis(tetrahydropyranyl ether) as a clear oil, $R_F = 0.6$ (ethyl acetate).

To a solution of the bis(tetrahydropyranyl ether) (320 mg.) in dry toluene (15 ml.) under an atmosphere of nitrogen at −78° C. was added 0.86 ml. of 1.95M solution of di-isobutyl aluminium hydride in toluene. After 15 minutes, the reaction was quenched by the dropwise addition of methanol (3 ml.) and after a further 15 minutes

at room temperature a mixture of 1:1 v/v saturated brine/water (25 ml.) was added, and the mixture was extracted with ethyl acetate (3 × 50 ml.). The extract was washed with saturated brine, and dried, and the solvents were exaporated to give the lactol, 4β - [4 - (3 - chlorophenoxy) - 3α - (tetrahydropyran - 2 - yloxy) - 1 - *trans*-butenyl] - 2,3,3aβ,6aβ - terahydro - 2 - hydroxy - 5β - (tetrahydropyran - 2 - yloxy)-cyclopenteno[b]furan, $R_F = 0.3$ (25% v/v ethyl acetate in methylene dichloride).

A stirred solution of (4-carboxybutyl)triphenylphosphonium bromide (6.21 g.) in dry toluene (125 ml.) was treated under argon at 90° C. with potassium-butoxide (3.01 g.) to form a solution of the corresponding ylide. The ylide solution (22.3 ml.) was then added to a solution of the lactol (388 mg.) in dry toluene (5 ml.) at room temperature. The mixture was stirred for 40 minutes, then water (1 ml.) was added. The toluene was evaporated, and the residual gum was partitioned between diethyl ether (4 × 10 ml.) and water (4 ml.). The aqueous layer was separated, acidified with 2N oxalic acid to pH 4, and extracted with a 1:1 v/v mixture of diethyl ether and pentane (6 × 15 ml.). The combined extracts were washed with brine, dried over magnesium sulphate and filtered, and the solvent was evaporated to give the required bis(tetrahydropyranyl ether), 16 - (3 - chlorophenoxy)9α - hydroxy - 11β,15α - bis-(tetrahydropyran - 2 - yloxy) - 17,18,19,20 - tetranor - 5 - *cis*,13 - *trans* - prostadienoic acid, $R_F = 0.5$ (ethyl acetate).

Example 2.

The process described in Example 1 was repeated, using the corresponding 11β,15β-bis(tetrahydropyranyl ether) as starting material, to give 16-(3-chlorophenoxy) - 9α,11β,15β - trihydroxy - 17,18,19,20 - tetranor - 5 - *cis*,13 - *trans*-prostadienoic acid, $R_F = 0.3$ (3% acetic acid in ethyl acetate). The n.m.r. spectrum (in deuterated acetone) showed the following characteristic bands (δ values):—

6.9—7.3, broad multiplets, 4 aromatic protons,
5.2—6.1, broad multiplets, 4 olefinic and 4 exchangeable protons,
4.0—4.6 broad multiplets, 5H, $>CH$. O— protons

The mass spectrum of the tetra(trimethylsilyl) derivative showed $(M—CH_3)^+ = 697.2970$, (calculated for $C_{34}H_{61}ClO_5Si_4 = 697.3001$).

The bis(tetrahydropyranyl ether) used as starting material may be obtained by the sequence of steps described in the second part of Example 1, starting from 4β-[4-(3 - chlorophenoxy) - 3α - (tetrahydropyran - 2 - yloxy) - 1 - *trans* - butenyl]-2,3,3aβ,6aβ - tetrahydro - 2 - oxo - 5α - (tetrahydropyran - 2 - yloxy) - cyclopenteno-[b]furan, *via* the following intermediates:

"bis-benzoate ester", $R_F = 0.6$ (5% v/v ethyl acetate in methylene dichloride)
"diol", $R_F = 0.4$ (ethyl acetate). The n.m.r. spectrum in deuterated acetone showed the following characteristic bands (δ values):
6.8—7.6, broad multiplets, 4 aromatic protons,
5.8—6.0, 2 olefinic protons,
3.7—5.2, broad multiplet, 5H, $>CH$. O— protons
"bis(tetrahydropyranyl ether)", $R_F = 0.6$ (25% v/v ethyl acetate in methylene dichloride)
"lactol", $R_F = 0.3$ (25% v/v ethyl acetate in methylene dichloride).

Example 3.

The process described in Example 1 was repeated, using 16-(3-chlorophenoxy)-9-oxo - 11β,15α - bis(tetrahydropyran - 2 - yloxy) - 17,18,19,20 - tetranor - 5 - *cis*,13-*trans*-prostanoic acid as starting material, to give 16-(3-chlorophenoxy)-11β,15α-dihydroxy-9-oxo-17,18,19,20-tetranor-5-*cis*,13-*trans*-prostadienoic acid, $R_F = 0.4$ (2.5% acetic acid in ethyl acetate). The n.m.r. spectrum (in deuterated acetone) showed the following characteristic bands (δ values):

6.9—7.2, broad multiplets, 4 aromatic protons,
5.2—6.1, broad multiplets, 4 olefinic and 3 exchangeable protons,
3.95—4.6, 4H, $>—CH$. O— protons

The mass spectrum of the 1,11,15-tris(trimethylsilyl)-9-methoxyimino derivative showed $M^+ = 667.2936$, (calculated for $C_{32}H_{54}ClNO_6Si_3 = 667.2946$).

The bis(tetrahydropyranyl ether) used as starting material may be obtained as follows:

A solution of 16 - (3 - chlorophenoxy) - 9α - hydroxy - 11β,15α - bis(tetrahydropyran - 2 - yloxy) - 17,18,19,20 - tetranor - 5 - *cis*,13 - *trans* - prostadienoic acid (92 mg.) in acetone (5 ml.) at 0° C. was treated with 8N chromic acid (50.4 μl.) for 25 minutes. Isopropanol was added, and the solution was diluted with ethyl acetate (50 ml.), washed with brine and dried. Evaporation of the solvent gave the required

9-oxo-bis(tetrahydropyranyl ether), $R_F = 0.4$ (5% v/v methanol in methylene dichloride).

Example 4.

The process described in Example 3 was repeated, using the corresponding 11β,15β-bis(tetrahydropyranyl ether) as starting material, to give 16-(3-chlorophenoxy) - 11β,15β - dihydroxy - 9 - oxo - 17,18,19,20 - tetranor - 5 - *cis*,13 - *trans*-prostadienoic acid, $R_F = 0.5$ (2.5% v/v acetic acid in ethyl acetate). The n.m.r. spectrum (in deuterated acetone) showed the following characteristic bands (δ values):

5.9—7.2, broad multiplets, 4 aromatic protons,

5.2—6.1, broad multiplets, 4 olefinic and 3 exchangeable protons,

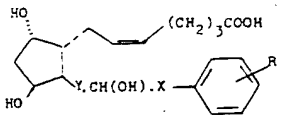
3.95—4.6, 4H, >*CH*.O— protons

The mass spectrum of the 1,11,15-tris(trimethylsilyl)-9-methoxyimino derivative showed $M^+ = 667.2928$, (calculated for $C_{32}H_{54}ClNO_6Si_3 = 667.2946$).

The bis(tetrahydropyranyl ether) used as starting material may be obtained by oxidation of the corresponding 9α-hydroxy 11β,15β-bis(tetrahydropyranyl ether) described in Example 2, by the process described in the second part of Example 3, $R_F = 0.4$ (5% v/v ethyl acetate in methylene dichloride).

Example 5.

The process described in Example 1 was repeated, using the appropriate bis(tetrahydropyranyl ether) as starting material to give the compounds shown in the table below. Mass spectrum data for the tetra(trimethylsilyl) derivatives. R_F values, for thin layer chromatography on silica gel, eluted with ethyl acetate, are also given for the corresponding diol intermediates of the formula VI.



R	Y	X	Mass spectrum		Diol of the formula VI
			Found	Calculated	
3-trifluoromethyl	*trans*-vinylene	CH_2O	$M^+ = 746.3492$	746.3458	$R_F = 0.4$
hydrogen	*trans*-vinylene	CH_2	$(M-CH_3)^+ = 647.3431$	647.3441	$R_F = 0.2$
4-chloro	*trans*-vinylene	CH_2O	$(M-CH_3)^+ = 697.2913$	697.2999	$R_F = 0.2$
3-chloro	ethylene	CH_2O	$M^+ = 714.3371$	714.3391	$R_F = 0.3$

In the manufacture of the compound wherein Y is an ethylene radical, the required starting material is obtained as follows:

A mixture of epimers (epimers at C—3 of the butenyl side-chain) of 4β-[4-(3-chlorophenyl) - 3 - hydroxybut - 1 - *trans* - enyl] - 2,3,3aβ,6aβ - tetrahydro - 2-oxo - 5α - (*p* - phenylbenzoyloxy) - cyclopenteno[b]furan (1.83 g.) was dissolved in ethanol (28 ml.) and the solution was added to nickel boride, previously prepared from nickel acetate (3.5 g.) and sodium borohydride (551 mg.). The mixture was shaken with hydrogen for 4 hours and was then filtered, and the filtrate was evaporated to dryness to give a mixture of epimeric saturated alcohols, 4β-[4-(3-chlorophenoxy-3-hydroxybutyl] - 2,3,3aβ,6aβ - tetrahydro - 2 - oxo - 5α - (*p* - phenylbenzoyloxy)-cyclopenteno[b]furan, $R_F = 0.3$ (50% v/v ethyl acetate in toluene). The mixture of epimeric saturated alcohols (1.47 g.) was stirred vigorously for 2½ hours with finely powdered anhydrous potassium carbonate (1.02 g.) in methanol (40 ml.). 1N Hydrochloric acid (15 ml.) was added, followed by ethyl acetate (200 ml.). The organic layer was separated, washed successively with saturated sodium bicarbonate solution and brine, and dried, the solvents were evaporated, and the residue was chromatographed on "Florisil" (trade mark) magnesium silicate (50 g.). Elution with diethyl ether

removed by-products, and subsequent elution with ethyl acetate gave a mixture of the corresponding saturated epimeric diols, $R_F = 0.3$ (ethyl acetate).

Example 6.

To a solution of the more polar C—15 epimer of 16-(3-chlorophenoxy)-9α,11β,15α - trihydroxy - 17,18,19,20 - tetranor - 5 - *cis*,13 - *trans* - prostadienoic acid (59 mg.) in methanol (1 ml.) at 0° C. was added an excess of a solution of diazomethane in diethyl ether. After 10 minutes, the solvents were evaporated to give the single C—15 epimer, methyl 16 - (3 - chlorophenoxy) - 9α,11β,15α - trihydroxy-17,18,19,20 - tetranor - 5 - *cis*,13 - *trans* - prostadienoate as a clear oil $R_F = 0.15$ (ethyl acetate) $(M—CH_3)^+ = 639.2754$, (calculated for $C_{31}H_{52}ClO_6Si_3 = 639.2760$).

Example 7.

A solution of methyl 16 - (3 - chlorophenoxy) - 9α,11β,15α - trihydroxy-17,18,19,20 - tetranor - 5 - *cis*,13 - *trans* - prostadienoate (14 mg.) in a mixture of diethyl ether (1ml.)and tetrahydrofuran (1 ml.) was added to a suspension of lithium aluminium hydride (25 mg.) in diethyl ether (3 ml.). The mixture was stirred at room temperature for 1 hour, the excess of hydride was destroyed by the addition of water (1 ml.) and the mixture was extracted with ethyl acetate. The extract was dried, and the solvent was evaporated to give 16-(3-chlorophenoxy)-17,18,19,20-tetranor-5-*cis*,13-*trans*-prostadien-1,9α,11β,15α-tetra-ol, $R_F = 0.5$ (10% methanol in ethyl acetate). The mass spectrum of the tetra(trimethylsilyl) derivative showed $M^+ = 698.3412$, (calculated for $C_{34}H_{63}ClO_5Si_4 = 698.3441$).

Example 8.

To a solution of methyl 16 - (3 - chlorophenoxy) - 9α,11β,15α - trihydroxy-17,18,19,20 - tetranor - 5 - *cis*,13 - *trans* - prostadienoate (22 mg.) in 1,2-dimethoxyethane (2 ml.) were added successively methyl iodide (1 ml.) and sodium hydride (2.25 mg. of a 60% w/v suspension in oil), and the mixture was stirred at room temperature for 2 hours. The solvents were evaporated under reduced pressure, and the residue was shaken with a mixture of ethyl acetate (3 × 15 ml.) and water (3 ml.). The organic phases were separated, combined and dried, the solvent was evaporated and the residue was purified by thin layer chromatography on silica gel plates, using ethyl acetate as the developing solvent, to give methyl 16 - (3 - chlorophenoxy) - 9α,11β-dihydroxy - 15α - methoxy - 17,18,19,20 - tetranor - 5 - *cis*,13 - *trans* - prostadienoate, $R_F = 0.30$ (ethyl acetate). The mass spectrum of the bis(trimethylsilyl)derivative showed $(M—CH_3)^+ = 581.2490$, (calculated for $C_{29}H_{46}ClO_6Si_2 = 581.2521$).

Example 9.

To a solution of 16 - (3 - chlorophenoxy) - 11β,15α - dihydroxy - 9 - oxo-17,18,19,20 - tetranor - 5 - *cis*,13 - *trans* - prostadienoic acid (24 mg.) in methanol (3 ml.) was added sodium borohydride (15 mg.). After 15 minutes, the reaction was quenched by the addition of aqueous oxalic acid, and the mixture was extracted with methylene dichloride (2 × 50 mls.). The extracts were combined, washed with saturated brine, and dried, and the solvents were evaporated to give a crude product which was esterified using an excess of diazomethane in diethyl ether (2 ml.). The methyl ester was purified by chromatography on 1.5 g. of silica gel, using ethyl acetate as eluent, to give methyl 16 - (3 - chlorophenoxy) - 9β,11β,15α - trihydroxy - 17,18,19,20-tetranor - 5 - *cis*,13 - *trans* - prostadienoate, $R_F = 0.30$ (50% acetone/methylene dichloride). The mass spectrum of the tris(trimethylsilyl) derivative showed $(M—CH_3)^- = 639.2798$, (calculated for $C_{31}H_{52}ClO_6Si_3 = 639.2758$).

Example 10.

The process described in Example 9 was repeated, using the corresponding 11β,15β-isomer as starting material, to give methyl 16-(3-chlorophenoxy)-9β,11β,15β-trihydroxy-17,18,19,20-tetranor-5-*cis*,13-*trans*-prostadienoate, $R_F = 0.33$ (50% v/v acetone in methylene chloride).

Example 11.

A solution of 9α - hydroxy - 11β,15 - bis(1 - methoxy - 1 - methylethoxy) - 15-(4 - trifluoromethylphenyl) - 16,17,18,19,20 - pentanor - 5 - *cis*,13 - *trans* - prostadienoic acid (123 mg.) in 0.8 ml. of pH 3 citric acid buffer and 1.8 ml. of acetone was stirred at room temperature for 18 hours. The solvents were evaporated and the residue was extracted with ethyl acetate (3 × 3 ml.). The extracts were combined, washed with a 1:1 v/v mixture of saturated brine and water, and were then dried.

After evaporation of the ethyl acetate, the residue consisted of a mixture of the C—15 epimers of 9α,11β,15 - trihydroxy - 15 - (4 - trifluoromethylphenyl) - 16,17,18,19,20-pentanor - 5 - *cis*,13 - *trans* - prostadienoic acid. Chromatography of this residue on CC4 Malinkrodt (trade mark) silica gel (2 g.), and elution with acetone/cyclohexane gave the separated C—15 epimers of 9α,11β,15-trihydroxy-15-(4-trifluoromethylphenyl)-16,17,18,19,20-pentanor-5-*cis*,13-*trans*-prostadienoic acid, $R_F = 0.15$ and 0.20 (2.5% v/v acetic acid in ethyl acetate). The n.m.r. spectrum of each epimer (in deuterated acetone) showed the following characteristic bands (δ values):

7.65, 4 aromatic protons

5.4—6.1, 5H, 4 olefinic protons and·PhC*H*(OH) . CH=CH—

4.2—4.9, 6H, C—9, C—11 and 4 exchangeable protons.

The mass spectrum of the tetra(trimethylsilyl) derivative showed $M^+ = 716.3353$, (calculated for $C_{34}H_{59}F_3O_5Si_4 = 716.3394$).

The bis-ether used as starting material may be prepared as follows:

To a solution of 2,3,3aβ,6aβ-tetrahydro-5β-hydroxy-4β-[3-hydroxy-3-(4-trifluoromethylphenyl)-1-*trans*-propenyl]-2-oxocyclopenteno[b]furan (250 mg.) (prepared by the process described in the second part of Example 1) in methylene dichloride (4 ml.), under an atmosphere of nitrogen, were added successively redistilled 2-methoxypropene (528 mg.) and a solution of anhydrous toluene-*p*-sulphonic acid in tetrahydrofuran (0.073 ml. of a 1% w/v solution). After 25 minutes, pyridine (2 drops) was added, followed by ethyl acetate (30 ml.). The solution was washed successively with saturated sodium bicarbonate and saturated brine and was dried. Evaporation of the solvents gave a mixture of epimeric 1-methoxy-1-methylethyl ethers as a clear oil, $R_F = 0.65$ (ethyl acetate).

To a solution of the epimeric ether (260 mg.) in dry toluene (17 ml.) under an atmosphere of nitrogen at −78° C., was added 0.75 ml. of a 1.95 m mole/ml. solution of di-isobutyl aluminium hydride in toluene. After 30 minutes, the reaction was quenched by the dropwise addition of methanol (2 ml.), and after a further 15 minutes at room temperature, a mixture of 1:1 v/v saturated brine/water (15 ml.) was added, and the mixture was extracted with ethyl acetate (3 × 25 ml.). The extract was washed with saturated brine and dried, and the solvents were evaporated to give a mixture of epimers of the lactol, 2,3,3aβ,6aβ - tetrahydro - 2 - hydroxy - 5β - (1 - methoxy-1 - methylmethoxy) - 4β - [3 - (1 - methoxy - 1 - methylethoxy) - 3 - (4 - trifluoromethylphenyl) - 1 - *trans* - propenyl] - cyclopenteno[b]furan, $R_F = 0.15$ (40% ethyl acetate/toluene).

A solution of the lactol (260 mg.) in toluene (7 ml.) was added to a solution of potassium 5-triphenyl-phosphoranylidenevalerate prepared from 1 mole of (4-carboxybutyl)triphenyl phosphonium bromide with 2 moles of potassium t-butoxide in toluene. The solution was stirred for 1 hour, and the solvent was removed by evaporation under reduced pressure. The residue was shaken with water (5 ml.) and diethyl ether (3 ml.) the aqueous layer was separated and extracted with diethyl ether(4 × 3 ml.) and the extracts were discarded. The aqueous solution was acidified to pH 5.5 with oxalic acid and extracted with a mixture of equal parts of diethyl ether and petroleum ether (b.p. 40—60° C.) (6 × 4 ml.). The combined extracts were washed with saturated brine and dried, and evaporation of the solvents gave 9α-hydroxy-11β,15-bis-(1-methoxy-1-methylethoxy) - 15 - (4 - trifluoromethylphenyl) - 16,17,18,19,20 - pentanor - 5-*cis*,13-*trans*-prostadienoic acid. $R_F = 0.38$ (10% v/v methanol in methylene chloride).

Example 12.

The process described in Example 1 was repeated, using the corresponding 11β,15-bis(tetrahydropyranyl ether) as starting material, to give the C—15 epimers of 16 - (3 - chlorophenoxy) - 9α,11β,15 - trihydroxy - 16 - methyl - 18,19,20 - trinor-5-*cis*,13-*trans*-prostadienoic acid, $R_F = 0.15$ and 0.20 (2.5% v/v acetic acid in ethyl acetate).

The mass spectrum of the tetra(trimethylsilyl) derivative showed $M^- = 725.3224$, (calculated for $C_{36}H_{65}ClO_6Si_4 = 725.3312$).

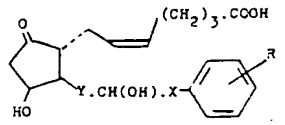
The bis(tetrahydropyranyl ether) used as starting material may be obtained as follows:

To a solution of 4β - [4 - (3 - chlorophenoxy) - 3 - hydroxy - 4 - methylpent-1 - *trans* - enyl) - 2,3,3aβ,6aβ - tetrahydro - 2 - oxo - 5α - (4 - phenylbenzoyloxy)-cyclopenteno[b]furan (1.97 g.) in methylene dichloride (36 ml.) were added successively 2,3-dihydropyran (3.3 ml.) and a solution of anhydrous toluene-*p*-sulphonic acid in tetrahydrofuran (1.8 ml. of a 1% w/v solution). After 10 minutes, pyridine (1 ml.) was added, followed by ethyl acetate (200 ml.). The solution was washed successively with sodium bicarbonate solution and brine, and was dried. Evaporation of the solvents

gave the epimeric tetrahydropyranyl ether as a clear oil, $R_F = 0.5$ (20% v/v ethyl acetate in methylene dichloride). To a solution of the epimeric tetrahydropyranyl ether (2.0 g.) in methanol (50 ml.) was added finely powdered anhydrous potassium carbonate (648 mg.). The mixture was stirred vigorously for 6 hours, then 1N hydrochloric acid (7 ml.) was added, followed by ethyl acetate (200 ml.). The organic layer was separated, washed successively with saturated sodium bicarbonate solution and brine and dried, and the solvents were evaporated. The residue was chromatographed on "Florisil" (trade mark) magnesium silicate (40 g.). Elution with diethyl ether removed the by-products, subsequent elution with ethyl acetate gave a mixture of the C—15 epimers of 4β - [4 - (3 - chlorophenoxy) - 4 - methyl - 3 - (tetrahydropyran - 2-yl)pent - 1 - *trans* - enyl] - 2,3,3aβ,6aβ - tetrahydro - 5α - hydroxy - 2 - oxo - cyclopenteno[b]furan, $R_F = 0.25$ (40% v/v ethyl acetate in methylene chloride). The process described in the latter part of Example 1 was repeated, using the above compound in place of the diol.

Example 13.

The process described in Example 3 was repeated, using the appropriate 9-oxo-bis(tetrahydropyranyl ether) as starting material, to give the derivatives shown in the following table.



R	Y	X	Mass Spectrum	
			Found	Calculated
3-trifluoromethyl	*trans*-vinylene	CH_2O	$M^- = 701.3202$	702.3210 (a)
hydrogen	*trans*-vinylene	CH_2	$M^+ = 617.3338$	617.3388 (a)
4-chloro	*trans*-vinylene	CH_2O	$(M-CH_3)^+ = 623.2438$	623.2433 (b)
3-chloro	ethylene	CH_2O	$M^+ = 640.2850$	640.2823 (b)
3-chloro	*trans*-vinylene	$C(CH_3)_2O$	$M^+ = 695.3240$	695.3260 (a)

(a) – for 9-methoxyimino-tris(trimethylsilyl) derivative

(b) – for 9-oxo-ris(trimethylsilyl) derivative

Example 14.

A solution of 11β,15 - bis(1 - methoxy - 1 - methylethoxy) - 9 - oxo - 15-(4 - trifluoromethylphenyl) -16,17,18,19,20 - pentanor - 5 - *cis*,13 - *trans* - prostadienoic acid (143 mg.) in a mixture of 0.7 ml. of pH 3 citric acid buffer and 2.1 ml. of acetone was stirred at room temperature for 18 hours. The solvents were evaporated, and the residue was extracted with ethyl acetate (3 x 20 ml.). The extracts were combined, washed with a 1:1 mixture of saturated brine and water, and then dried. After evaporation of the ethyl acetate, the residue consisted of a mixture of the C—15 epimers of 11β,15 - dihydroxy - 9 - oxo - 15 - (4 - trifluoromethylphenyl)-16,17,18,19,20 - pentanor - 5 - *cis*,13 - *trans* - prostadienoic acid, $R_F = 0.45$ (2½% v/v acetic acid in ethyl acetate). The n.m.r. spectrum (in deuterated acetone) showed the following characteristic bands (δ values):

7.67, 4 aromatic protons,
5.3—6.3, 4 olefinic protons,
C_{15} proton and 3 exchangeable protons

The mass spectrum of the bis(trimethylsilyl)-9-methoxyimino-methyl ester showed

$M^+ = 671.3080$, (calculated for $C_{32}H_{52}F_3NO_5Si_3 = 671.3104$).

The 9-oxo-bis-ether used as starting material may be obtained as follows:

A solution of 9α - hydroxy - 11β,15 - bis - (1 - methoxy - 1 - methylethoxy)-15 - (4 - trifluoromethylphenyl) - 16,17,18,19,20 - pentanor - 5 - *cis*,13 - *trans*-prostadienoic acid (200 mg.) in methylene dichloride (2 ml.) was added to a stirred solution of Collins' reagent, prepared from chromium trioxide (280 mg.) and pyridine (0.45 ml.) in methylene dichloride (5 ml.). After 15 minutes at room temperature the mixture was extracted with ether (2 × 10 ml.), and the combined extracts were washed with saturated brine and dried. Evaporation of the solvents gave the required 9-oxo-bis-ether, $R_F = 0.43$ (10% v/v methanol) in methylene chloride).

Example 15.

16-(3-Chlorophenoxy)-9α,11β,15α-trihydroxy-17,18,19,20-tetranor-5-*cis*,13-*trans*-prostadienoic acid	250 μg.
Sodium citrate B.P.	30.5 mg.
Citric acid, anhydrous, B.P.	2.8 mg.
Sodium chloride, Ph.Eur.	35.0 mg.
Water for injections, Ph.Eur. to	5.0 ml.

The sodium citrate, citric acid and sodium chloride are dissolved in most of the water, the 16 - (3 - chlorophenyl) - 9α,11β,15α - trihydroxy - 17,18,19,20 - tetranor-5-*cis*,13-*trans*-prostadienoic acid is added, and the solution is made up to volume with water for injections. The solution is filtered to remove particulate matter, filled into neutral glass ampoules and autoclaved, to give an injectable pharmaceutical or veterinary composition.

The prostadienoic acid derivative may, of course, be replaced by an equivalent amount of another prostadienoic acid derivative of the invention.

Example 16.

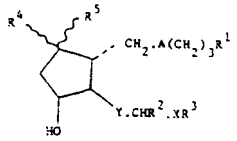
	% w/v
15-(4-trifluoromethylphenoxy)-9α,11β,15α-trihydroxy 16,17,18,19,20-pentanor-5-*cis*,13-*trans*-prostadienoic acid	0.003
Sodium phosphate	2.90
Sodium hydrogen phosphate	0.30
Water for injection	to 100

The sodium phosphate was dissolved in about 80% of the water, followed by the prostadienoic acid derivative, and, when dissolved, the sodium hydrogen phosphate. The solution was made up to volume with water for injection, and the pH was checked to be between 6.7 and 7.7. The solution was filtered to remove particulate matter, sterilised by filtration, and filled into pre-sterilised neutral glass ampoules under aseptic conditions. Immediately before use, the contents of an ampoule are diluted in sodium chloride B.P. for administration by intravenous infusion.

The prostadienoic acid derivative may, of course, be replaced by an equivalent amount of another prostanoic acid derivative of the invention.

WHAT WE CLAIM IS:—

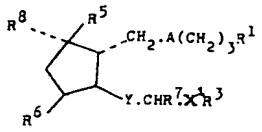
1. A process for the manufacture of an 11-*epi*-prostanoic acid derivative of the formula:



wherein either R^1 is a carboxy or hydroxymethyl radical or an alkoxycarbonyl radical of up to 11 carbon atoms, R^4 is a hydroxy radical and R^5 is a hydrogen atom, or R^1 is a carboxy radical or an alkoxycarbonyl radical of 2 to 11 carbon atoms and R^4 and R^5 together form an oxo radical, R^2 is a hydroxy radical or an alkoxy radical of 1 to 4 carbon atoms, Y is an ethylene or *trans*-vinylene radical, either A is an ethylene or vinylene radical, and X is an alkylideneoxy radical of 1 to 6 carbon atoms wherein the alkylidene is bonded to —CHR^2 and the oxygen is bonded to R^3, or an alkylene

radical of 1 to 6 carbon atoms, or A is a vinylene radical and X is a direct bond and R^3 is a phenyl or naphthyl radical which is unsubstituted or which bears one or two substituents selected from halogen atoms, nitro, hydroxy, phenyl or trifluoromethyl radicals, alkyl, alkenyl or alkoxy radicals each of up to 5 carbon atoms, or dialkylamino radicals wherein each alkyl is of 1 to 3 carbon atoms, and, for those compounds wherein R^1 is the carboxy radical, the pharmaceutically or veterinarily acceptable salts thereof, which comprises:

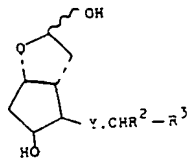
(a) for those compounds wherein R^1 is a carboxy radical, R^4, when it is a hydroxy radical, is in the α-configuration and X is other than a direct bond, the hydrolysis of the compound of the formula:—



II

wherein R^1, R^3, A and Y have the meanings defined above, X′ has any of the meanings given above for X except a direct bond, R^6 is a tetrahydropyran-2-yloxy or C_{4-10} alkoxydialkylmethoxy radical, R^7 is an alkoxy radical of 1 to 4 carbon atoms or a tetrahydropyran-2-yloxy of C_{4-10} alkoxydialkylmethoxy radical, and either R^8 is a hydroxy radical or a tetrahydropyran-2-yloxy radical and R^5 is a hydrogen atom, or R^8 and R^5 together form an oxo radical; or R^6 is R^5 is a β-hydrogen atom, A is a vinylene radical and X is a direct bond, the a hydroxy radical or an aroyloxy radical of up to 15 carbon atoms, R^7 is hydroxy radical and R^8 is an aroyloxy radical of up to 15 carbon atoms, whereafter when a salt is required, the product so obtained is reacted with a base; or

(b) for those compounds wherein R^1 is a carboxy radical, R^4 is an α-hydroxy radical, R^5 is a β-hydrogen atom, A is a vinylene radical and X is a direct bond, the reaction of a lactol of the formula:



III

wherein R^2 and R^3 have the meanings defined above, with a (4-carboxybutyl)-triphenylphosphonium salt, in the presence of a strong base, whereafter when a salt is required, the product so obtained is reacted with a base; or

(c) for those compounds wherein R^1 is an alkoxycarbonyl radical, the reaction of the corresponding compound of the formula I wherein R^1 is a carboxy radical, with a diazoalkane of 1 to 10 carbon atoms, or of a salt thereof with an alkyl halide; or

(d) for those compounds wherein R^1 is a hydroxymethyl radical, R^4 is a hydroxy radical and R^5 is a hydrogen atom, the reduction of a corresponding compound of the formula I wherein R^1 is an alkoxycarbonyl radical; or

(e) for those compounds wherein R^2 is an alkoxy radical, the reaction of the corresponding compound of the formula I wherein R^2 is a hydroxy radical with an alkyl halide of 1 to 4 carbon atoms in the presence of a strong base; or

(f) for those compounds wherein A is a *trans*-vinylene radical, the separation of a mixture comprising the said compound wherein A is a *trans*-vinylene radical and the corresponding compound wherein A is a *cis*-vinylene radical.

2. An 11-*epi*-prostanoic acid derivative of the formula I given in claim 1, wherein R^1, R^2, R^3, R^4, R^5, A, X and Y have the meanings stated in claim 1.

3. An 11-*epi*-prostanoic acid derivative as claimed in claim 2 wherein R^1 is a carboxy, hydroxymethyl, methoxycarbonyl, ethoxycarbonyl, butoxycarbonyl, hexyloxycarbonyl or decyloxycarbonyl radical, R^2 is a hydroxy, methoxy, ethoxy, propoxy or butoxy radical, A, Y, R^4 and R^5 have the meanings stated in claim 1, X is a direct bond or a methyleneoxy, ethyleneoxy, isopropylideneoxy, 1-methyl propylideneoxy, 1-ethylpropylideneoxy, methylene, ethylidene, isopropylidene, propylidene, 1-methylpropylidene, 1-ethylpropylidene, ethylene, 1-methylethylene, [—$CH(CH_3)CH_2$—], 1,1-dimethylethylene [—$C(CH_3)_2 . CH_2$—], 2-methylethylene [—$CH_2 . CH(CH_3)$—] or trimethylene radical, and R^3 is chloro-, bromo-, fluoro-, nitro-, hydroxy-, phenyl-,

trifluoromethyl-, methyl-, ethyl-, propyl-, allyl-, methoxy-, ethoxy-, propoxy-, or dimethylamino- phenyl or -naphthyl radical, and for those compounds wherein R^1 is a carboxy radical, the ammonium, alkylammonium containing 1 to 4 alkyl substituents each of 1 to 4 carbon atoms, alkanolammonium containing 1 to 3 2-hydroxyethyl radicals, and alkali metal salts thereof.

4. An 11-*epi*-prostanoic acid derivative as claimed in claim 2 or 3 wherein R^1 is a carboxy, hydroxymethyl or methoxycarbonyl radical, A is a *cis*-vinylene radical, R^4, R^5 and Y have the meanings stated in claim 1, R^2 is a hydroxy or methoxy radical, X is a direct bond or a methyleneoxy or methylene radical, and R^3 is a phenyl, chlorophenyl or trifluoromethylphenyl radical.

5. An 11-*epi*-prostanoic acid derivative as claimed in claim 2 wherein R^1 is a carboxy or hydroxymethyl radical, or an alkoxycarbonyl radical of up to 11 carbon atoms, and R^2, R^3, R^4, R^5, A, X and Y have the meanings stated in claim 1.

6. An 11-*epi*-prostanoic acid derivative as claimed in any one of claims 2 to 5, wherein R^1 is a carboxy, hydroxymethyl, methoxycarbonyl or ethoxycarbonyl radical, R^2 is a hydroxy radical, A is a *cis*-vinylene radical, Y is a *trans*-vinylene radical, X is a direct bond or a methyleneoxy radical and R^3 is a chlorophenyl or trifluoromethylphenyl radical.

7. An 11-*epi*-prostanoic acid derivative as claimed in any one of claims 2 to 6 wherein X is a methyleneoxy radical and R^3 is a 3-chlorophenyl or 3-trifluoromethylphenyl radical.

8. An 11-*epi*-prostanoic acid derivative as claimed in any one of claims 2 to 6 wherein X is a direct bond and R^3 is a 4-trifluoromethylphenyl radical.

9. An 11-*epi*-prostanoic acid derivative as claimed in claim 2 which is 16-(3-chlorophenoxy) - 9α,11β,15α - trihydroxy - 17,18,19,20 - tetranor - 5 - *cis*,13 - *trans*-prostadienoic acid, 16 - (3 - chlorophenoxy) - 9β,11β,15α - trihydroxy - 17,18,19,20-tetranor - 5 - *cis*,13 - *trans* - prostadienoic acid, methyl 16 - (3 - chlorophenoxy)-9α,11β,15α - trihydroxy - 17,18,19,20 - tetranor - 5 - *cis*,13 - *trans* - prostadienoate, 16 - (3 - chlorophenoxy) - 17,18,19,20 - tetranor - 5 - *cis*,13 - *trans* - prostadien-1,9α,11β,15α - tetraol, 16 - (3 - chlorophenoxy) - 11β,15 - dihydroxy - 9 - oxo 17,18,19,20 - tetranor - 5 - *cis*,13 - *trans* - prostadienoic acid or 9α,11β,15α - trihydroxy - 15 - (4 -trifluoromethylphenyl) - 16,17,18,19,20 - pentanor - 5 - *cis*,13-*trans* - prostadienoic acid.

10. An 11-*epi*-prostanoic acid derivative as claimed in any one of claims 2 to 9 which is in racemic form.

11. An 11-*epi*-prostanoic acid derivative as claimed in any one of claims 2 to 9 which is in a luteolytically-effective optically-active form.

12. A pharmaceutical or veterinary composition comprising an 11-*epi*-prostanoic acid derivative as claimed in claim 1 together with a pharmaceutically or veterinarily acceptable diluent or carrier.

13. An 11-*epi*-prostanoic acid derivative as claimed in claim 2 substantially as hereinbefore described in any one of Examples 1 to 14.

14. An 11-*epi*-prostanoic acid derivative as claimed in claim 5 substantially as hereinbefore described in any one of Examples 1 to 4.

15. A composition as claimed in claim 12 substantially as hereinbefore described in Examples 15 of 16.

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